WORKPLACE EXPOSURE TO ETS AND LUNG CANCER:

PRESENTATION ON META-ANALYSIS FINDINGS

Paul S. Levy, Sc.D
Professor of Epidemiology and Biostatistics
School of Public Health
University of Illinois at Chicago

December 1, 1998

For presentation at the meeting of the NTP Board of Scientific Counselors, Report on Carcinogens Subcommittee, December 2-3, 1998, Research Triangle Park, North Carolina 27709.

Dr. Levy's time and expenses in preparation for this presentation are reimbursed by R.J. Reynolds Tobacco Company. This report reflects solely his independent work and opinions on this topic and, in no way, should be construed to represent opinions held by the University of Illinois at Chicago, R.J. Reynolds, or any other Institution.

INTRODUCTION

There are in the published literature approximately 50 epidemiological studies (such as those mentioned in Chapter 3 of the draft NTP Background Document) on environmental tobacco smoke and lung cancer. Risk ratios or odds ratios generated from these studies are generally low, more often above than below unity, and have 95% confidence intervals that most often overlap unity, thus indicating no statistical significance. The lack of statistical significance obtained from most of these studies has resulted in the use of meta-analysis techniques to help gain insight into whether there is indeed a statistical association.

The NTP Draft Background Document cites several meta-analyses, including a recently published meta-analysis by A. Judson Wells on studies of ETS exposure in the workplace and lung cancer. I have analyzed the Wells 1998 publication cited in the NTP Draft Background Document. Also, I have performed similar meta-analyses of the U.S. workplace ETS and lung cancer epidemiology studies. Most previous meta-analyses of the workplace ETS studies have used most, if not all, of the available studies and have used the published statistics without adjustment. These previous meta-analyses by other investigators (three mentioned in Dr. Wells' paper plus myself) have found summary odds ratios close to unity with confidence intervals overlapping unity.[1] (Exhibit 1)

WELLS 1998 META-ANALYSIS

In performing his meta-analysis, Wells scrutinized the published odds ratios and confidence intervals, investigated those that he considered "suspicious", and made several

---

[1]My meta-analysis was performed on all U.S. workplace ETS studies, representing 11 of the 18 data sets available worldwide.

corrections to the published statistics. Using a fixed effects model, Wells found a summary odds ratio for the 18 data sets used in his analysis (12 U.S.; 6 elsewhere) of 1.19 (95% CI:1.07 to 1.34) that was statistically significant.

Wells made several changes to the odds ratios and/or confidence intervals as originally published. Most of his changes were minor and had little impact on the meta-analysis of the ETS workplace studies. However, Dr. Wells did make substantial changes to two studies (Janerich 1990 and Fontham 1994). These changes by Wells are largely responsible for his increased summary odds ratios that differ from prior meta-analyses.

Wells modified the 95% confidence intervals for the Janerich study. The original 95% confidence intervals were 0.80 to 1.04. Wells' "correction" to these confidence intervals are 0.61 to 1.35. I have made an additional adjustment to Wells' CIs to account for the fact that Janerich used individually matched case-control pairs in his study. My modified 95% confidence intervals are 0.77 to 1.41.

Janerich 1990 Confidence Intervals

As published	.91 (95% CI: 0.80-1.04)
Wells recalculation	.91 (95% CI: 0.61-1.35)
Levy correction to Wells recalculation	.91 (95% CI: 0.77-1.41)

The original Fontham publication reported crude workplace odds ratio of 1.12 and an adjusted odds ratio of 1.39. Wells did not use the values from the original Fontham publication and instead used an odds ratio of 1.56 recalculated by Reynolds that had eliminated non-working women and controlled for additional covariates. The adjusted workplace odds ratio in the Reynolds' recalculation is questionable because 1) it is

considerably higher than the odds ratio found in the same study for total household exposure; and 2) it is higher than the crude odds ratio, in spite of the fact that the confounder control should result in a lower rather than a higher odds ratio. For these two reasons, I used the Reynolds' version of the crude odds ratio in my reanalysis of the Wells' meta-analysis. On the basis of the data in her published letter, I calculated a crude odds ratio of 1.40.

Fontham 1994 Odds Ratios

	Crude	Adjusted
As published	1.12	1.39
Reynolds recalculation	1.40	1.56

Using Wells' recalculated figures, the summary odds ratios that would be obtained from the 12 U.S. data sets used by Wells (he did not report U.S. findings separately) are 1.19 (95% CI: 1.04 to 1.36) for a fixed effects model and 1.16 (95% CI: 0.97 to 1.34) for a random effects model. The fixed effects model yields a statistically significant OR; however the random effects model does not. (Exhibit 2)

REANALYSIS OF WELLS META-ANALYSIS

In my re-analysis of the Wells' meta-analysis, I also included the workplace odds ratio from the Stockwell study (cited in the NTP Draft Background Document), not published in the original article, but subsequently calculated by Dr. Ron Marks. I also made the corrections to Dr. Wells' figures for the Fontham and Janerich studies as indicated above. My re-analysis of the Wells' meta-analysis is shown in Exhibit 3. The resulting odds ratio for U.S. workplace studies of 1.13 (95% CI: 1.00 to 1.28) for the

fixed effects model is just barely significant and the odds ratio of 1.12 (95% CI: 0.97 to 1.34) for the random effects model is not significant.

DISCUSSION

In pursuing meta-analysis on observational studies such as those that have examined ETS and lung cancer, it is very important to avoid either overweighting or underweighting specific studies. The fixed effects model weights according to the inverse of the estimated variance of the odds ratio, which is subject to considerable variability itself. Use of the random effects model can ameliorate the effects of this type of instability. Using Wells' figures, the random effects model in a meta-analysis does not result in a statistically significant relationship between ETS in the workplace and lung cancer.

Another major limitation in Dr. Wells' published workplace meta-analysis is that he excluded in his primary analysis certain studies based on his post-hoc review of the studies. As a result, the main thrust of his article, Table 1, included data from only 6 of the 18 data sets available at the time and only 25% of the available lung cancer cases. Wells' meta-analysis effectively gives a weight of zero to several major studies, including the highly regarded Brownson 1992 study which had a workplace OR of 0.98 (95% CI: 0.74-1.31).

CONCLUSIONS

1. The size of the estimated meta-analytic odds ratios and confidence intervals were very sensitive to judgments concerning the appropriate data points to use in meta-

analysis. This is another example of the fragility of the use of meta-analysis in estimating low-level associations.

2. The random effects method gave more conservative confidence intervals than the fixed effects and is generally the method of choice in combining odds ratios from studies having diverse protocols and controlling for different covariates.

3. In all of these meta-analyses, the resulting summary odds ratios are very low. This makes them sensitive to biases from confounding that have been discussed at length in many forums.

Exhibit 1. Workplace Meta-Analysis on U.S. Studies Performed by Levy in 1997 and Based on Original Publications or Data Appearing in Butler (cited in Wells 1998)

	Study	Gender	Design	Rate Ratio	L95	U95
1	Kabat,1984	m	CaCo	3.27	1.01	10.6
2	Kabat,1984	f	CaCo	0.68	0.32	1.47
3	Garfinkel,1985	f	CaCo	0.93	0.55	1.55
4	Wu, 1985	f	CaCo	1.3	0.5	3.3
5	Butler, 1988	f	Cohort	1.72*	0.3*	3.4*
6	Janerich,1990	Both	CaCo	0.91	0.80*	1.04*
7	Brownson, 1992	f	CaCo	0.79	0.61*	1.03
8	Fontham 1994	f	CaCo	1.39*	1.11*	1.74*
9	Kabat, 1995	m	CaCo	1.02	0.5	2.09
10	Kabat, 1995	f	CaCo	1.15	0.62	2.13
11	Schwartz, 1996	f	CaCo	1.5	1	2.2

* = different number from that used by Wells

Summary Odds Ratios (95% Confidence Intervals)

Fixed Effects Model: OR=1.02 (0.92 to 1.12)

Random Effects Model: OR = 1.11 (0.91 to 1.34)

Exhibit 2. **Workplace Meta-Analysis on U.S. Data Sets Used by Wells and Based on Wells' Updated Data**

	Study	Gender	Design	Rate Ratio	L95	U95
1	Kabat,1984	m	CaCo	3.27	1.01	10.6
2	Kabat,1984	f	CaCo	0.68	0.32	1.47
3	Garfinkel,1985	f	CaCo	0.93	0.55	1.55
4	Wu, 1985	f	CaCo	1.3	0.5	3.3
5	Butler, 1988	m	Cohort	1	0.3	3.4
6	Butler, 1988	f	Cohort	1.2	0.3	6.1
7	Janerich,1990	Both	CaCo	0.91	0.61	1.35
8	Brownson, 1992	f	CaCo	0.98	0.74	1.31
9	Fontham (Reynolds), 96	f	CaCo	1.56	1.21	2.02
10	Kabat, 1995	m	CaCo	1.02	0.5	2.09
11	Kabat, 1995	f	CaCo	1.15	0.62	2.13
12	Schwartz, 1996	f	CaCo	1.5	1	2.2

Summary Odds Ratios (95% Confidence Intervals)

Fixed Effects Model: OR=1.19 (1.04 to 1.36)

Random Effects Model: OR = 1.16 (0.97 to 1.34)

Exhibit 3. **Workplace Meta-Analysis on U.S. Studies Used in Levy's Original Analysis with the Addition of the Stockwell Study. Values of Odds Ratios and Confidence Intervals are those Used by Wells with the Exception of the Janerich and Fontham Studies which Use Levy's Corrections to Wells' Published Figures**

	Study	Gender	Design	Rate Ratio	L95	U95
1	Kabat,1984	m	CaCo	3.27	1.01	10.6
2	Kabat,1984	f	CaCo	0.68	0.32	1.47
3	Garfinkel,1985	f	CaCo	0.93	0.55	1.55
4	Wu, 1985	f	CaCo	1.3	0.5	3.3
5	Butler, 1988	m	Cohort	1	0.3	3.4
6	Butler, 1988	f	Cohort	1.2	0.3	6.1
7	Janerich,1990	Both	CaCo	0.91	0.77	1.41
8	Brownson, 1992	f	CaCo	0.98	0.74	1.31
9	Fontham (Reynolds), 1996	f	CaCo	1.4	1.11	1.76
10	Kabat, 1995	m	CaCo	1.02	0.5	2.09
11	Kabat, 1995	f	CaCo	1.15	0.62	2.13
12	Schwartz, 1996	f	CaCo	1.5	1	2.2
13	Stockwell, 1992	f	CaCo	0.93	0.64	1.37

Summary Odds Ratios (95% Confidence Intervals)

Fixed Effects Model: OR=1.13 (1.00 to 1.28)

Random Effects Model: OR = 1..12 (0.96 to 1.34)